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Cytokine regulation of host protection against infectious diseases

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The discoveries that T cells can secrete different sets of cytokines, termed type 1 (Th1) and type 2 (Th2) cytokines, and that recovery from infection with the intracellular protozoan parasite, *Leishmania major*, depends on the production of type 1 rather than type 2 cytokines, demonstrated that a vertebrate host can produce a specific cytokine response and that recovery from disease requires the host to make a specific cytokine response. The observation, made a few years later, that recovery from infection with the gastrointestinal worm, *Trichuris muris*, depends on production of type 2 cytokines and is inhibited by type 1 cytokines, demonstrated that the same cytokine response is not protective under all circumstances. A host, thus, needs to be able to recognize pathogen characteristics sufficiently well to generate the appropriate protective cytokine response. Studies of hosts infected with any of several different pathogens suggest that the pathogen recognition capacity of the host immune system is limited to two main classes, epitomized by *L. major* and *T. muris*, and that it protects against these classes by making a type 1 or type 2 cytokine response, respectively. More recent observations indicate that the inflammatory responses stimulated by type 1 or type 2 cytokines are both complex and stereotyped, in that they includes multiple effector mechanisms that provide an umbrella of protection against an entire pathogen class. For example, IFN-g, the key type 1 cytokine, induces the transcription of over 200 genes. Although these genes stimulate effector mechanisms, including production of NO, production of IGTP, stimulation of vitamin D synthesis, and stimulation of granuloma formation, that protect against pathogens as diverse as influenza virus, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Leishmania major* and *Toxoplasma gondii*, different IFN-g-dependent effector mechanisms appear to protect against the different pathogens in this group. Similarly, studies in mice infected with different gastrointestinal nematode parasites, such as *Nippostrongylus brasiliensis*, *Trichinella spiralis*, *Trichuris muris*, *Heligmosomoides polygyrus*, and *Strongyloides venezuelensis*, demonstrate that each of these parasites induces an IL-4/IL-5/IL-9/IL-13 response. These cytokines, in turn, stimulate a stereotyped inflammatory response that includes eosinophilia, mastocytosis, goblet cell hyperplasia, IgE secretion, increased responsiveness of target cells to inflammatory mediators, increased smooth muscle contractility and changes in epithelial absorption, secretion, and permeability. All elements of this stereotyped “type 2” inflammatory response protect against at least one member of this group; however the entire “type 2” inflammatory response is not required to protect against any single one of these nematode parasites. Taken together with the observation that type 1 cytokines suppress type 2 cytokine-induced effector mechanisms and vice versa, these observations suggest that the limited abilities of the vertebrate host to identify pathogen susceptibilities has led to an evolutionary compromise. Because the host is able to distinguish pathogens susceptible to “type 1” inflammation from those susceptible to “type 2” inflammation, pathogen suppression is maximized and host self-damage minimized by allowing “type 1” and “type 2” responses to be mutually suppressive; because the host cannot reliably identify the specific susceptibilities of individual pathogens within the “type 1” or “type 2” class, it generates “type 1” or “type 2” inflammatory responses that are sufficiently broad to defend against most members of each pathogen class, even though the breadth of the inflammatory response generated does unnecessary damage to the host.